Continuous cerebrovascular reactivity monitoring in moderate/severe traumatic brain injury: a narrative review of advances in neurocritical care

Frederick A. Zeiler 1,2,3,4,*, Ari Ercole 2, Marek Czosnyka 5,6, Peter Smielewski 5, Gregory Hawryluk 1, Peter J. A. Hutchinson 7, David K. Menon 2 and Marcel Aries 8

1Section of Neurosurgery, Department of Surgery, Rady Faculty of Health Sciences, Winnipeg, Canada, 2Division of Anaesthesia, Department of Medicine, University of Cambridge, Cambridge, UK, 3Biomedical Engineering, Faculty of Engineering, Winnipeg, Canada, 4Department of Human Anatomy and Cell Science, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada, 5Section of Brain Physics, Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK, 6Institute of Electronic Systems, Warsaw University of Technology, Warsaw, Poland, 7Division of Neurosurgery, Department of Clinical Neurosciences, Addenbrooke’s Hospital, University of Cambridge, Cambridge, UK and 8Department of Intensive Care, Maastricht UMC, Maastricht, the Netherlands

*Corresponding author. E-mail: Frederick.Zeiler@umanitoba.ca

Summary

Impaired cerebrovascular reactivity in adult moderate and severe traumatic brain injury (TBI) is known to be associated with worse global outcome at 6–12 months. As technology has improved over the past decades, monitoring of cerebrovascular reactivity has shifted from intermittent measures, to experimentally validated continuously updating indices at the bedside. Such advances have led to the exploration of individualised physiologic targets in adult TBI management, such as optimal cerebral perfusion pressure (CPP) values, or CPP limits in which vascular reactivity is relatively intact. These targets have been shown to have a stronger association with outcome compared with existing consensus-based guideline thresholds in severe TBI care. This has sparked ongoing prospective trials of such personalised medicine approaches in adult TBI. In this narrative review paper, we focus on the concept of cerebral autoregulation, proposed mechanisms of control and methods of continuous monitoring used in TBI. We highlight multimodal cranial monitoring approaches for continuous cerebrovascular reactivity assessment, physiologic and neuroimaging correlates, and associations with outcome. Finally, we explore the recent ‘state-of-the-art’ advances in personalised physiologic targets based on continuous cerebrovascular reactivity monitoring, their benefits, and implications for future avenues of research in TBI.

Keywords: cerebral autoregulation; cerebrovascular reactivity; neurocritical care; traumatic brain injury

Cerebrovascular reactivity has emerged as a monitored physiologic parameter of interest in adult critically ill traumatic brain injury (TBI) patients, with support from recent multimodal monitoring (MMM) consensus statements.1-2 Given the inter-patient heterogeneity in cerebrovascular reactivity after TBI,3-6 the association with clinical outcome,7-9 and the relative lack of good therapies directed at dysfunction,7,10,11 there has emerged the desire and need for tailored therapeutic approaches. Such personalised therapies would require continuous cerebrovascular reactivity monitoring capabilities at the bedside,12-17 the ability to derive and display patient-specific physiologic metrics in real time,13,14 and the availability of autoregulation modulating therapies.13,15-17 Recent improvements in continuous cerebrovascular reactivity monitoring in TBI can facilitate detection and continuous monitoring of individualised autoregulation guided cerebral perfusion pressure (CPP) and intracranial pressure (ICP)
Although such individualised targets have been shown to be associated with improved outcomes retrospectively, the benefit of using these targets needs to be proven in prospective interventional randomised control trials. Although such trials would currently focus on manipulations of physiology and outcome improvement, an understanding of the biological basis for dysautoregulation could lead to the development of therapies that restore autoregulatory efficiency. Such understanding could emerge from studies of the molecular and genetic mechanisms involved in cerebral autoregulation in TBI.\(^{18}\) This could represent a major step towards personalised and precision medicine in moderate and severe TBI care.

---

**Fig 1.** Diagrammatic representation of cerebral autoregulatory curve and consequences of selected Pathology. (a) The classic ‘Lassen’ curve showing the relationship between CPP and CBF (black line). The grey line is suggested to be the autoregulation curve in a cohort of patients with long-standing hypertension. The LLA and the ULA are shifted to the right. In addition, the plateau might decrease compared with intact cerebral autoregulation cohort. (b) Compared with the classic ‘Lassen’ autoregulation curve (black line), the autoregulation curve of severe TBI patients with generalised cerebral edema might look like the grey curve. The LLA is shifted to the right and the ULA is shifted to the left resulting in a smaller plateau. In addition, the slopes of the different parts are likely steeper and the plateau has shifted downwards indicating a lower absolute perfusion state. (c) Compared with the classic ‘Lassen’ curve (black line) totally impaired cerebral autoregulation can be represented by a steep (grey) line. No autoregulation plateau is present and CBF is following changes in CPP passively. CBF, cerebral blood flow; CPP, cerebral perfusion pressure; LLA, lower limit of autoregulation; TBI, traumatic brain injury; ULA, upper limit of autoregulation.
The following review explores continuous cerebrovascular reactivity monitoring in adult TBI, highlighting the background, theories of control, methods of monitoring, clinical literature, the move towards personalised physiologic targets during current neurocritical care management, and future directions of research.

## Defining cerebral autoregulation

### Definition

Cerebral autoregulation refers to the ability of the cerebral vascular system to maintain relatively constant levels of cerebral blood flow (CBF), despite changes in systemic MAP or CPP. The concept of cerebral autoregulation was first described by Fog,[19] in controlled CBF assessments in cats, and Lassen[20] through observational studies of CBF in humans during different CO2 and MAP manipulations. Both described the static phenomenon of the cerebral vessels innate ability to regulate CBF to a constant level, across different levels in MAP.[20] Of note, given the technical limitations of the time, such descriptions did not use continuously updating assessments based on slow-wave vasogenic fluctuations, which are now emerging as the main method for continuous bedside assessment. Since Fog[19] and Lassen[20], various studies in preclinical experimental models[21–27] and humans[8,9,28–33] have described the concept of cerebral autoregulation, and outline different methods of assessment.[34–36] Fig. 1 shows our conceptual understanding of cerebral autoregulation and the relationship between CBF and MAP, during both healthy and various diseased states related to TBI.

### Classic theories of cerebral blood flow control

In general, the brain arterial bed can be divided to conducting and regulating arteries/arterioles. Small precapillary arterioles are believed to be the key vessels involved in cerebral autoregulation, measuring up to a few hundred microns in diameter, and representing the main site where active vasoconstriction and dilatation takes place.[37–39] Typically occurring in the slow-wave vasogenic frequency range of 0.05–0.005 Hz.[31,40] The mechanisms involved in the control of cerebrovascular tone, and thus vasoregulatory capacity, have been detailed in various other publications.[18,33,41–44]

Table 1 provides an account of the various theorised mechanisms involved in CBF control in humans. In general, four main classical mechanisms[38,41,42] of CBF control have emerged: myogenic, endothelial, neurogenic, and metabolic. The myogenic mechanism is predicated on the notion that slow changes in flow induce shear stress and vascular smooth muscle stretch lead to reflex alterations in smooth muscle tone, and thus vessel diameter, controlling CBF.[55–57] This theory relies on smooth muscle stretch receptors and calcium based sarcoplasmic changes leading to variations in smooth muscle function. The endothelial mechanism revolves around shear stress operating on the endothelial lining of cerebral vessels, leading to induced changes in vascular mediator expression, including but not limited to factors such as nitric oxide synthase (NOS) and endothelin (ET).[59–61] These mediators lead to change in cerebrovascular tone, and thus CBF. The neurogenic mechanisms involve the direct neural input for vasomotor control, as mediated by various neurotransmitters such as adrenergic/noradrenergic, dopaminergic, serotonergic, and cholinergic based transmitters.[13,52–56] It is postulated that through various

### Table 1

<table>
<thead>
<tr>
<th>Classical theory of control</th>
<th>Hypothetical main players</th>
<th>Summary of mechanism</th>
<th>Limitations of theory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myogenic</td>
<td>Calcium channels</td>
<td>Limited to reflex mediated control of vascular tone in response to changes in CBF. Unlikely to occur in isolation.</td>
<td>Does not account for known stretch-mediated smooth muscle response seen in cerebral vessels.</td>
</tr>
</tbody>
</table>

The concept of cerebral autoregulation was first described by Fog,[19] in controlled CBF assessments in cats, and Lassen[20] through observational studies of CBF in humans during different CO2 and MAP manipulations. Both described the static phenomenon of the cerebral vessels innate ability to regulate CBF to a constant level, across different levels in MAP.[20] Of note, given the technical limitations of the time, such descriptions did not use continuously updating assessments based on slow-wave vasogenic fluctuations, which are now emerging as the main method for continuous bedside assessment. Since Fog[19] and Lassen[20], various studies in preclinical experimental models[21–27] and humans[8,9,28–33] have described the concept of cerebral autoregulation, and outline different methods of assessment.[34–36] Fig. 1 shows our conceptual understanding of cerebral autoregulation and the relationship between CBF and MAP, during both healthy and various diseased states related to TBI.
synapses of the nervi vasorum, such as direct sympathetic and parasympathetic inputs, vascular tone may be quickly mediated in response to slow changes in driving pressure, leading to control of CBF. Finally, the metabolic mechanism suggests that changes in local metabolite concentrations matched to CBF lead to proportional smooth muscle response. However, the time frame for metabolic changes being the sole regulator of cerebral vascular tone is not in keeping with the rapidity of blood vessel response to changes in driving pressure. Fig. 2 provides a diagrammatic representation of the main CBF control mechanisms, both classical and emerging.

Aside from the classical ‘mechanical’ theories of CBF control, emerging literature suggests the role of other processes in the development of impaired vascular reactivity. Recently, the role for inflammatory cytokines, mediators of blood–brain barrier (BBB) dysfunction, autonomic nervous system, and cortical spreading depression (CSD) have all been raised as potential players in the impaired vascular reactivity seen after TBI. These aspects are beyond the scope of this review, but are touched upon briefly, with references, in Appendix A of the online Supplementary material.

Methods of monitoring autoregulation in traumatic brain injury

Several approaches have been used for the quantitative assessment of cerebral autoregulation in TBI. These methods have been categorised in various ways according to the physiological signals used to derive autoregulatory metrics, the monitoring techniques used to detect these, and the temporal and spatial resolution of the metrics that are derived. The nomenclature system in the literature organises autoregulation measurements into those which are intermittent in nature (imaging based metrics) and those that are robust enough to be applied continuously (ICP or near-infrared
Continuous autoregulation monitoring

Continuous measures of cerebral autoregulation/cerebrovascular reactivity are seen as the desired method for cerebral monitoring in critically ill TBI patients. Various simple input–output methods exist, including frequency and time domain based continuous metrics. However, the most commonly described and used methodologies in adult TBI involve time domain based assessments of the relationship between spontaneous slow-wave fluctuations in a continuously measured surrogate of cerebral blood volume (CBV) or CBF as output variables, and a driving pressure for flow as an input variable (MAP or CPP). The slow-wave vasogenic frequency range of 0.05–0.005 Hz has been identified as the frequency range for cerebrovascular responses related to changes in MAP. In order to assess cerebrovascular reactivity from raw signals, the following general time domain process is followed. First, both the continuous surrogate measures of CBV/CBF and MAP/CPP are captured from bedside monitors at typically 50 Hz or higher frequency. Next, a 10 s average filter is applied to both signals to decimate it to 0.1 Hz, limiting the influence of faster slow frequencies related to breathing. Next, using moving Pearson linear correlation coefficients, typically based on 30 consecutive (10 s averaged) values updated every minute (i.e. 5 min of data, updated every minute), an index of cerebrovascular reactivity is derived. The classic, and most commonly used, example in adult TBI is the pressure reactivity index (PRx), which is derived from the moving correlation between slow waves of ICP (surrogate of change in CBV) and MAP (surrogate of changes in the driving pressure). In general, cerebrovascular reactivity index values that are positive denote ‘impaired’ autoregulation and describe passive transition of driving pressure influence on CBV. Values that are negative or around zero are believed to denote ‘intact’ autoregulation by active filtering the transition of slow waves. Fig. 3 provides a diagrammatic representation of the calculation method for PRx from raw high-frequency physiologic data. Furthermore, these continuously updating methods have led to the ability to derive individual physiologic targets in adult TBI. The next section will discuss in more detail various continuous cerebrovascular reactivity measures currently described in the adult TBI literature.
Currently used continuous monitors of cerebrovascular reactivity in adult traumatic brain injury

Continuous multimodal monitoring metrics

Based on the concept of evaluating the relationship between spontaneous slow-wave vasogenic fluctuations in signals, as described above, various measures of cerebrovascular reactivity can be derived using a range of invasive and noninvasive continuous MMM used in the assessment of critically ill TBI patients. The currently described techniques include those cerebrovascular reactivity indices derived from: ICP, transcranial Doppler (TCD), NIRS, brain tissue oxygen (PbtO$_2$), and thermal diffusion CBF (TD-CBF) monitoring. Appendix C of the online Supplementary material provides an overview of the different cerebral monitoring devices, and the related cerebrovascular reactivity metrics.

The signal based metrics can be divided into three main classes: (1) those that are based on surrogate measure of changes in CBV, (2) those based on surrogate measures of changes in CBF, and (3) those based on cerebral physiologic metrics other than CBV or CBF. As highlighted by three recent retrospective cohort studies in adult TBI, these continuous indices are not all equivalent, nor do they all measure the same aspect of the cerebrovascular reactivity process. To date, only a few metrics have been validated as a measure of autoregulation experimentally. We will focus on these, with the remaining MMM metrics described in Appendix C of the online Supplementary material.

Intracranial pressure and near-infrared spectroscopy monitoring

ICP and NIRS monitoring provide the most commonly applied CBV-based metrics of continuous cerebrovascular reactivity. ICP-based indices are considered the ‘standard’ by many experts in the field given the robust signals and experimental literature supporting them (see next section). They provide global information regarding cerebrovascular reactivity using the ICP$^2$ or the pulse amplitude of ICP (AMP)$^2,23$ as a surrogate of slow changes in CBV. Lower resolution metrics for ICP-derived cerebrovascular reactivity indices exist, but are not commonly used clinically, and are beyond the scope of this review. Appendix D of the online Supplementary material provides a brief description of these low-resolution metrics and the relevant associated literature.

Bifrontal NIRS measurement information regarding changes in oxygenated and deoxygenated haemoglobin that are caused by changes in CBV is used to calculate cerebrovascular reactivity. The theory behind this is that an increase in intracranial volume is compensated by arterial or venous components. In comatose patient with low metabolic activity, we therefore expect the total Hb, as the sum of oxygenated and deoxygenated Hb, to remain constant. In case of multi-channel NIRS application, regional vasoregulation or homeostatic information is obtained. NIRS also may provide some information regarding the contribution of changes in CBF, but differentiation from accompanying CBV changes at the same time is difficult. Both ICP and NIRS indices have, to some extent, been validated in experimental animal models (see next section).

Experimental validation studies

Of all the described continuous cerebrovascular reactivity measures in adult TBI, very few have received pre-clinical experimental validation as true measures of autoregulation in animal models. To date, only ICP-based PRx, PAx (correlation between AMP and MAP), and RAC (correlation [R] between AMP [A] and CPP [C]) have data to support that they can detect the lower limit of autoregulation (LLA) during arterial hypotension and intracranial hypertension. NIRS based THx (or HVx; correlation between total haemoglobin index [THI] and CPP) and total oxygenation index (TOx or COx; correlation between total oxygen index [TOI] or regional oxygen saturation [rSO$_2$] and CPP) have only been assessed in experimental arterial hypotension, confirming that these measures provide information regarding the LLA. All other intracranial based metrics have either never been evaluated experimentally against the LLA or upper limit of autoregulation (ULA), or have displayed inconclusive results. Of note, there are currently no data which document that these continuous metrics of cerebrovascular reactivity reliably measure the ULA, as such validation is subject to model limitations (i.e. animals succumbing to cardiac failure prior to MAP reaching and surpassing the ULA). This aspect requires further exploration.

Physiologic and outcome associations with continuously measured cerebrovascular reactivity in traumatic brain injury

Given the myriad of cerebrovascular reactivity metrics available, the literature on this topic in adult TBI can be daunting. In the following section, we summarise the important literature regarding associations between continuously measured cerebrovascular reactivity and both cerebral physiologic measures and patient outcome. For simplicity, we will focus on the MAP (input) and CBV/ICP (output)-derived measures (mainly PRx), given the extensive literature on these measures, their acceptance by the international community, and existence of experimental data supporting them as measures of the LLA.

Association with patient and injury factors

Continuously measured PRx has been evaluated in various studies in adult TBI. Specific recurring associations between patient demographics have been identified. First, advanced age appears to be associated with worse autoregulatory function in moderate/severe TBI, with those above the age of 60 yr demonstrating the worst measures. Second, although the data are limited, there is some suggestion that females younger than 50 yr display worse cerebrovascular reactivity after moderate/severe TBI compared with their male counterparts (males, PRx 0.044 [sd 0.031]; females, PRx 0.11 [0.047]; P<0.05), although this finding requires validation with control for co-variates. Third, low admission Glasgow Coma Scale (GCS) score was associated with poor cerebrovascular reactivity during the ICU monitoring period (r=0.29; P<0.01). Fourth, admission intracranial injury burden, as assessed using CT, has been demonstrated to be associated with worse cerebrovascular reactivity during the acute ICU stay. In particular, specific injury patterns associated with acceleration/deceleration or shearing mechanisms display the strongest link to globally impaired vascular reactivity. Such injury characteristics...
include presence of a subdural haematoma, traumatic subarachnoid haemorrhage, and sub-cortical diffuse axonal injury. These findings suggest that these particular high energy injury mechanisms appear to predispose adult TBI patients to develop sustained impaired cerebrovascular reactivity during their ICU stay. Finally, admission Acute Physiology, Age, Chronic Health Evaluation II (APACHE II) scores, but not injury severity scores, are strongly associated with impaired cerebrovascular reactivity metrics.98 This suggests that the extracranial injury burden is not necessarily an additional driver of impaired vascular reactivity, but the individual systemic stress response to trauma may drive impaired cerebrovascular reactivity. These findings raise questions as to the role of the autonomic nervous system,52,54,99 inflammatory mediators,59,100,101 and TBI therapeutic interventions (e.g. deep sedation, fluids, cooling, transfusion)10,11,102 in the acute phase, in driving impaired autoregulation in TBI. Further investigation of all of the above patient and injury factors is ongoing as part of the CENTER-TBI High Resolution ICU Sub-Study objectives.

Association with continuously monitored cerebral physiology

There have been a large number of studies assessing the correlation and association between cerebrovascular reactivity monitoring and other continuously measured cerebral physiology in adult moderate/severe TBI.12,103,104 Elevated ICP has been well documented to be associated with worse cerebrovascular reactivity,12,103,104 and appears to be a key physiologic driver of ongoing impairment. CPP values at both upper and lower extremes are associated with worse cerebrovascular reactivity,105 and form the basis for individualised CPP targets or target range in adult TBI care, summarised as the ‘optimal’ CPP concept. This refers to the concept of a ‘safe’ autoregulation plateau (see following sections for further discussion).13,17,105,106 The specific CPP thresholds associated with impaired vascular reactivity are individual and dynamic, and are related to combinations of physiologic factors, such as ICP, chronic systemic hypertension, and degree of baseline

Fig 4. Example of CPPopt determination in traumatic brain injury (TBI). This recording in a patient with severe TBI is a snapshot of 4 h period from a recording of several days with invasive ABP and ICP monitoring. Illustration of time series of ABP (a) and ICP (b). (c) Mean PRx values are plotted in 5 mm Hg bins of CPP in this 4 h period; this yields a parabolic or U-shaped curve. The minimum of the PRx indicates the point of best-preserved autoregulation—CPP ‘optimal’ (CPPopt=86 mm Hg)—and is the nadir of the fitted curve. Constructing such 4 h parabolic curves and automated CPPopt values forms the basis of the CPPopt methodology (as described by Aries and colleagues’). (d) The trends of patients’ CPP value (straight line) and CPPopt (dashed line) and also the deviation from CPPopt. To increase the yield and stability of the CPPopt trend a weighted multi-(calculation) window approach was developed and currently under investigation in the COGITATE study (as described by Beqiri and colleagues108). The histogram of time spent in certain CPP values (%) in the lowest panel (e) shows the maximum at lower CPP values, indicating that this patient was predominantly managed at a CPP lower than the ‘optimal’ level. ABP, arterial blood pressure; CPP, cerebral perfusion pressure; CPPopt, optimal CPP; ICP, intracranial pressures; PRx, pressure reactivity index (correlation between slow waves of ICP and ABP).
cardiovascular and pulmonary fitness. As such, these individualised CPP thresholds can be seen as a ‘moving’ value, dependent on patient baseline factors, and ongoing factors related to the injury and treatment.

In keeping with the relationship between CPP and PRx—although the number of clinical studies with invasive continuously measured CBF are limited—there does exist some preliminary data, using LDF or TD-CBF, to support the temporal relationship between reduced local CBF and impaired PRx measures. The relationship between other MMM physiologic variables and PRx in adult TBI are less commonly described. A brief overview of these findings and the relevant literature can be found in Appendix E of the online Supplementary material.

Association with outcome

Numerous studies confirm the association between continuously measured PRx and global outcome. Czosnyka and colleagues documented the first associations between continuously measured cerebrovascular reactivity in moderate/severe adult TBI and global outcome in 1997 ($r=0.48$; $P<0.00001$). This study has sparked various other retrospective assessments of cerebrovascular reactivity summarised over the whole monitoring period and its association with global patient outcome. One such (single-centre) study, evaluating 25 yr of neuro-monitoring in 1146 critically ill adult TBI patients, displayed the persistently strong association between outcome and PRx despite changes in BTF based guidelines over time. Moreover, PRx has distinct critical thresholds associated with poor global outcome at 6 months, including thresholds of 0, +0.25, and +0.35. The other ICP-derived cerebrovascular reactivity indices, PAx and RAC, also display critical thresholds associated with outcome. In addition, a recent retrospective analysis, controlling for admission demographics and other physiologic variables, has confirmed the persistently strong association between impaired cerebrovascular reactivity (measured as PRx, PAx, or RAC), with 6 month outcome. This study also displayed higher area under the receiver operating curve (AUC) for prognostic models including cerebrovascular reactivity indices, compared with baseline models with patient demographics, ICP, and CPP physiologic measures. These results suggest added prognostic value of vascular reactivity monitoring in adult TBI above standard ICP/CPP monitoring and call for new interventions. Furthermore, recent publications from the prospective multi-centre CENTER-TBI High Resolution ICU Sub-Study have confirmed the above-mentioned associations with outcome, providing additional confidence in the results from previous retrospective studies.

Current status of treatment for dysfunctional cerebrovascular reactivity in traumatic brain injury

Despite the strong links between impaired cerebrovascular reactivity and patient outcome, current BTF based therapies
pay limited attention to continuous updated vascular reactivity status. A large 25 yr retrospective single-centre study, analysing 1146 critically ill TBI patients with invasive ICP monitoring, provides some evidence to support the lack of BTF-based treatment effect on continuously measures cerebrovascular reactivity. Within this analysis, ICP, CPP and PRx were assessed in each patient across the archived ICU physiology recording period. Patients were split into 5 yr epochs, considering specific BTF guideline changes over these periods. The results clearly showed that ICP and CPP values were controlled in response to changing BTF based guidelines. However, PRx failed to demonstrate any substantial improvement across all assessed epochs. Given this context, it is interesting that the mortality rate for this cohort also remained relatively stable across the 25 yr. As a corollary, the prospective multi-centre CENTER-TBI High Resolution ICU Sub-Study has recently confirmed the relative independence of PRx to treatment measures in the ICU, as measured through daily therapeutic intensity level (TIL) total and sub-scores. This study also displayed the relative constant time spent with PRx above the value of 0 on a daily basis (as a measure of cerebrovascular reactivity impairment), at 40–50% per day during the first 7 days of ICU care, despite ongoing active care.

All these results are relevant in the face of the current lack of effective treatment for impaired cerebrovascular reactivity in adult TBI. As such, there is a need for future investigation into potential molecular targets aimed at prevention and treatment of impaired autoregulation. As we wait for such work to be conducted, we are currently left with the difficult situation of patient management in the absence of directed therapies. Consequently, current interest has moved towards individual personalised CPP targets in critically ill TBI patients, focussing on achieving CPP values associated with the ‘least–worst’ cerebrovascular reactivity status for a given patient. This concept forms the basis for ‘optimal CPP’ (CPPopt), which will be covered in detail within the next section.

State-of-the-art personalised cerebral perfusion pressure targets guided by cerebrovascular reactivity monitoring

The CPPopt concept has gained interest in the past decade with the observation that PRx and CPP often exhibit a U-shaped relationship over time with a minimum PRx occurring at a CPP above the value of 0 on a daily basis (as a measure of cerebrovascular reactivity impairment), at 40–50% per day during the first 7 days of ICU care, despite ongoing active care. As described above, the feasibility of a 4-hourly updated CPP target is currently tested in the prospective COGITO study. Irrespective of the published results, one might argue that a faster and continuous adaption of the CPP target (within preset safety ranges) might be more suitable and beneficial. This practise will probably prove to be very labour intensive and could trigger speculations about the use of an automated system which allows continuous delivery of drugs (e.g. noradrenaline) in a closed-loop system in a neurocritical care setting. However, it is important to be cautious about such approaches, because the time constants for changing autoregulation may be more rapid than the pharmacokinetic and pharmacodynamics temporal precision in which we can stabilise the MAP. Furthermore, our increasing understanding of autonomic influences on cerebral autoregulation may mean that autoregulation-guided CPP management is now underway to inform the design of any future phase III study in severe TBI patients (CPPopt Guided Therapy: Assessment of Target Effectiveness [COGITO]; clinicaltrials.gov identifier NCT02982212). Appendix F in the online Supplementary material displays an example CPPopt determination during COGITO and the data review steps and intervention.

Future of cerebrovascular reactivity monitoring in traumatic brain injury

Existing studies have focused on identifying one autoregulation-guided CPP target, ignoring the fact that a broader CPP range might provide similar autoregulation benefit. As depicted in Fig. 5, understanding the position and shape of CPP-PRx may help us identify the CPP below which PRx is impaired (the lower limit of reactivity [LLR]), the CPP above which PRx is again impaired (upper limit of reactivity [ULR]), and the CPP range associated with intact PRx (within limits of reactivity [WLR]). The time spent with CPP less than LLR and (10 mm Hg) deviation below CPPopt are significantly independently related to adverse outcome, fitting with the clinical maxim that periods with low CPP should be avoided in severe TBI patients. Similar to the recently developed visualisation method of the CPP-PRx landscape, the continuous estimation of CPP reactivity limits provides the clinician with more contextual information to the single CPPopt value and therefore may align better with clinical acumen. In this scenario, management based on the individual autoregulation-guided CPP could be a compromise between the aggressive CPP-oriented therapy promulgated by Rosner and colleagues and the more permissive Lund protocol. A recent nested randomised controlled study showed that keeping MAP above the individual LLA (using TCD-based mean flow index [Mx]) in cardiothoracic patients during cardiopulmonary bypass significantly reduced the incidence of postoperative delirium by 45%. As described above, the feasibility of a 4-hourly updated CPP target is currently tested in the prospective COGITO study. Irrespective of the published results, one might argue that a faster and continuous adaption of the CPP target (within preset safety ranges) might be more suitable and beneficial.
biology of dysautoregulation, however, may allow us to use interventions that reduce its incidence and severity, and thus reduce reliance on manipulation of systemic physiology as our sole therapeutic target.

Individual intracranial pressure thresholds

Aside from personalised CPP targets, the concept of individual ICP thresholds has emerged utilising continuously monitoring cerebrovascular reactivity, mainly PRx. Retrospective literature suggests the tolerance for derangements in ICP and CPP is directly impacted by autoregulatory status, with dose response (i.e. outcome) heat map patterns seen in adult TBI populations which support a higher tolerance for ICP elevations when autoregulation is preserved.12 Furthermore, although the literature remains in its infancy, two studies to date have displayed a stronger association between time spent above individual ICP threshold, compared with BTF guideline based ICP thresholds.14,121 The first study was a retrospective single-centre evaluation of manually determined individual ICP thresholds.12 This study explored the relationship between PRx and ICP, with the individual ICP threshold determined by direct visual inspection of the error bar plots where PRx becomes consistently higher than +0.20. The ICP value after which PRx remains higher than +0.20 for all higher ICP values is deemed the individual ICP threshold. The results of this analysis demonstrated that the dose above individual ICP threshold displayed the highest discriminatory value for dichotomised outcome prediction (AUC=0.81; 95% confidence interval [CI], 0.74–0.87) over both the dose of ICP above a fixed threshold of 20 and 25 mm Hg (AUC=0.75; 95% CI, 0.68–0.81 and AUC=0.77; 95% CI, 0.70–0.83, respectively).

The second study was a recent validation of data from the prospective multi-centre CENTER-TBI High Resolution ICU Sub-Study, in which a semi-automated algorithmic detection of the individual ICP threshold was developed, using the same criteria from the manual threshold study.121 This study used automated detection of the intersection between the locally weighted scatterplot smoothing (LOWESS) function of the PRx vs ICP relationship, and the line PRx=-0.20. Visual verification for each patient was conducted, making it semi-automatically. This study confirmed that approximately two-thirds of patients have an identifiable individual ICP threshold, whereas the mean hourly dose spent above individual ICP threshold displayed higher AUC (0.678, P=0.029) for outcome compared with dose of ICP of 20 or 22 mm Hg (AUC=0.509, P=0.03 and AUC=0.492, P=0.035, respectively). This effect was maintained with correction for baseline admission characteristics.

Despite these results, the application of individual ICP thresholds is unclear and requires further validation and improvement of automated detection algorithms. Furthermore, such thresholds have only been studied using the entire ICU recording period, leaving them currently for post-ICU long-term prognostication.15,14,121 If such thresholds are to be used clinically, moving window calculations will have to be developed, similar to CPPopt, allowing for continuously updating individual ICP threshold targets.

Development of therapeutic targets for impaired cerebrovascular reactivity

Our current treatment strategy for impaired cerebrovascular reactivity in adult moderate/severe TBI revolves around finding the ‘optimal’ CPP for which cerebrovascular reactivity indices indicated ‘intact’ autoregulation. However, there exists the need for therapies directed at reversing and preventing impaired autoregulation. As such, future studies on cerebrovascular reactivity in TBI will need to incorporate information from various sources, including those from the CNS systemic variables. Through using combinations of invasive/noninvasive MMM,1,12,121 both during the acute ICU and long-term follow-up phases of care, the relationship between continuously measured cerebrovascular reactivity and other important cerebral physiologic metrics can be uncovered and transformed into therapeutic targets. In the upcoming years, the link between continuously measured PbtO2, TD-CBF, ICP, CPP, cortical EEG, and cerebral metabolism, as assessed through cerebral microdialysis, may provide important insights into the relationships between cerebrovascular reactivity, CBF, BBB integrity and oxygen diffusion, autonomic response, CSD, and aerobic metabolism/mitochondrial function. In addition, systemic impairments associated with ventilation (e.g. \( P_{aCO_2} \)) and cardiac function are likely to influence cerebrovascular reactivity and might lead to targeted intervention studies.

Furthermore, integrating this high-frequency information with serum, microdialysis protein biomarkers of inflammation, or both, BBB integrity, and vascular function, may provide important insights into potential molecular pathways involved in impaired cerebrovascular reactivity and other cerebral physiologic dysfunction seen after moderate or severe TBI. In addition, including individual patient genome-wide association data may also uncover particular single nucleotide polymorphisms involved in CBF regulation and control during both the healthy and brain injured state, providing further information on potential molecular pathways driving autoregulatory dysfunction.18,61 Through combining all of these complex data, one may be able to determine individual therapeutic targets for impaired cerebrovascular reactivity in adult TBI, and develop therapies directed at prevention and treatment, reducing mortality in TBI. In addition, incorporating noninvasive NIRS or TCD based continuous cerebrovascular reactivity monitoring during follow-up clinic visits, combined with the complex physiologic and biological data obtained during the acute phase of care, we may be able to highlight the association between long-term clinical phenotype and persistent impairment of cerebrovascular reactivity. With knowledge of individual pathways involved in CBF control, gleaned from the acute phase data, persistent symptomatology related to cerebrovascular dysfunction may then be amendable to personalised therapeutics, with the goal of reducing long-term morbidity.

Conclusions

Over the previous decades, continuous cerebrovascular reactivity monitoring in adult critically ill TBI patients has emerged as an important physiologic metric, with strong links to global prognosis. Despite a lack of effective proven treatments directed at impaired cerebrovascular reactivity in TBI, continuous monitoring of this cerebral physiologic mechanism has led to important advancements in bedside care, with the availability of personalised CPP targets. Future research in cerebrovascular reactivity in adult TBI will revolve around improving personalised physiologic targets for ICU care, while exploring potential drivers of impaired vascular reactivity. The hope is that through integration of cerebral MMP, protein, imaging, and genetic biomarkers, the molecular mechanisms involved in cerebrovascular dysfunction after TBI will be
uncovered, leading to therapies directed at prevention and new treatments in the acute phase.

**Authors’ contributions**

Study concept, design, research, figure/artwork creation: FAZ, MA
Writing paper: all authors
Revising paper: AE, MC, PS, GH
Discussion: AE, MC, PS, GH, PJH, DKM

**Declaration of interest**

PS and MC have financial interests in a part of licencing fee for ICM+ software (Cambridge Enterprise Ltd, UK). DKM has consultancy agreements and/or research collaborations with GlaxoSmithKline, Ornim Medical, Shire Medical, Calico, Pfizer, Pressura, Glide Pharma, and NeuroTraumaSciences.

**Funding**

University of Manitoba Thorlakson Chair for Surgical Research Establishment Grant, University of Manitoba VPRi Research Investment Fund (RIF), Winnipeg Health Sciences Centre Foundation, and the University of Manitoba Rudy Falk Clinician–Scientist Professorship (to FAZ). NIHR (Research Professorship, Cambridge BRC and Global Health Research Group on Neurotrauma) (to PJH). National Institute for Healthcare Research (NIHR, UK) through the Acute Brain Injury and Repair theme of the Cambridge NIHR Biomedical Research Centre and a European Union Framework Program 7 grant (CENTER-TBI; Grant Agreement No. 602150).

**Appendix A. Supplementary data**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2019.11.031.

**References**


83. Oshorov A, Savin I, Popugaev K, Potopov A. Influence of hyperthermia on the parameters of MAP, CPP and PRx in patients with severe TBI. Brain Inj 2014; 28: 797


Handling editor: Jonathan Hardman